CEBP Focus: Update on Lymphoma

Benzene Exposure and Risk of Non-Hodgkin Lymphoma

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Abstract

Exposure to benzene, an important industrial chemical and component of gasoline, is a widely recognized cause of leukemia, but its association with non-Hodgkin lymphoma (NHL) is less clear. To clarify this issue, we undertook a systematic review of all case-control and cohort studies that identified probable occupational exposures to benzene and NHL morbidity or mortality. We identified 43 case-control studies of NHL outcomes that recognized persons with probable occupational exposure to benzene. Forty of these 43 (93%) studies show some elevation of NHL risk, with 23 of 43 (53%) studies finding statistically significant associations between NHL risk and probable benzene exposure. We also identified 26 studies of petroleum refinery workers reporting morbidity or mortality for lymphomas and all neoplasms and found that in 23 (88%), the rate of lymphoma morbidity or mortality was higher than that for all neoplasms. A substantial healthy-worker effect was evident in many of the studies and a comprehensive reevaluation of these studies with appropriate adjustments should be undertaken. Numerous studies have also reported associations between benzene exposure and the induction of lymphomas in mice. Further, because benzene is similar to alkylating drugs and radiation in producing leukemia, it is plausible that it might also produce lymphoma as they do and by similar mechanisms. Potential mechanisms include immunotoxicity and the induction of double-strand breaks with subsequent chromosome damage resulting in translocations and deletions. We conclude that, overall, the evidence supports an association between occupational benzene exposure and NHL. (Cancer Epidemiol Biomarkers Prev 2007;16(3):385–91)

Introduction

Benzene is an important industrial chemical, as evidenced by production in excess of 2 billion gallons annually in the United States, and is a component of gasoline. Workers in a number of industries, including petroleum refining, shipping, rubber manufacturing, automobile repair, and shoe manufacturing, are potentially exposed to high levels of benzene. Benzene exposures among the general public are lower than most occupational exposures and result from cigarette smoking, gasoline use, and automobile emissions. Although benzene is a widely recognized cause of leukemia, the association of benzene with non-Hodgkin lymphoma (NHL) is less clear. Given the prevalence of benzene exposure and the potential for benzene to produce chromosome changes and other genetic changes of importance in NHL induction, it is essential to clarify the association between benzene exposure and NHL. Accurate quantification of the burden of benzene-associated diseases is necessary to evaluate the health risk posed by environmental contamination and occupational exposures at current exposure limits. Toward this aim, we undertook a review of all case-control and cohort studies that identified probable occupational exposures to benzene and NHL morbidity or mortality and concluded that the evidence supports an association between occupational benzene exposure and NHL.

Early Case Reports of Benzene-Induced Lymphoma

In the early 1900s, benzene was widely used as an industrial solvent and through the appearance of multiple reports in the literature of anemia, pancytopenia, and leukemia, its toxicity to the blood and bone marrow quickly became manifest. French investigators were the first to report a case of lymphoma associated with benzene exposure in 1947 (1). Similar reports emerged in the 1960s from France, Italy, and Spain. Studies in Turkish shoe workers by Aksoy and others in the 1970s and 1980s were instrumental in establishing the relationship between benzene and leukemia, but these studies also identified 11 cases of lymphoma associated with occupational benzene exposure (2). They concluded that benzene could cause a variety of hematologic and lymphatic malignancies, in addition to damaging the bone marrow.

Solvent Exposure and NHL

As highlighted in this issue by Vineis and coworkers, occupational exposure to solvents has been associated with an increased risk of NHL in numerous studies. In their review on the topic, Rego et al. (3) considered that 72% of studies with an accurate definition of solvent exposure observed positive associations between solvent exposures and NHL. Solvents, however, are chemically diverse and often exist as chemical mixtures, which makes it difficult to incriminate a specific chemical agent (4). Given the association of benzene with disorders of the bone marrow and blood, and the ability of the chemical to produce chromosomal and genetic changes important to NHL induction, it is plausible that benzene is a specific solvent associated with NHL.

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M.T.S. has received consulting and expert testimony fees from law firms representing both plaintiffs and defendants in cases involving exposure to benzene.

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Table 1. Case control studies of NHL with benzene exposure

Author	Date	Study design	Findings	Comments
Bernard et al.	1984	Population-based, Yorkshire	RR, 4.21 (0.54-32.79)	NHL, men employed in the petroleum industry
			RR, 0.49 (0.21-2.00)	NHL, men who reported benzene use
Blair et al.	1993	Population-based, Iowa and Minnesota	OR, 1.1 (0.8-1.4)	NHL, exposure to low intensities of benzene
			OR, 1.5 (0.7-3.1)	NHL having had exposure to higher intensities of benzene
			OR, 1.9 (0.7-5.3)	Follicular NHL and exposure to higher intensities of benzene
			OR, 1.8 (0.6-5.4)	Diffuse NHL and exposure to higher intensities of benzene
			OR, 1.6 (0.5-5.8)	NHL, employment in petroleum refining industry
			OR, 1.1 (0.9-1.4)	NHL, potential exposure to benzene
Costantini et al.	2001	Population-based, Italy	N/A	No elevated odds ratios for job titles associated with benzene
Dryver et al.	2004	Registry-based, Sweden	OR, 1.45 (1.13-1.86)	NHL, job-related exposures to aromatic hydrocarbons
			OR, 1.92 (1.20-3.08)	NHL, exposure to gasoline for >5 y
Fabbro-PeRRay et al.	2001	Population-based, France	OR, 2.0 (1.1-3.9)	NHL, benzene exposure compared with no exposure
			OR, 2.3 (1.1-4.1)	NHL, benzene exposure >10 y ago compared with no exposure
			OR, 2.4 (0.9-5.9)	NHL, benzene exposure duration >15 y; trend with duration
			OR, 5.7 (1.4-23.2)	NHL, cumulatively exposed >810 d compared with never exposed
			OR, 1.7 (0.4-6.9)	NHL, exposed <810 d compared with never exposed
Franceschi et al.	1989	Hospital-based, Italy	RR, 1.14 (0.57-2.28)	NHL, exposure to benzene
			RR, 1.83 (0.87-3.84)	NHL, petroleum workers
Fritschi and Siemiatycki	1996	Population-based, Montreal	OR, 0.7 (0.4-1.1)	NHL, nonsubstantial benzene exposure (some opportunity for exposure)
			OR, 0.8 (0.3-2.1)	NHL, substantial benzene exposure (probable or definite exposure for 5+ y at high frequency)
Fritschi et al.	2005	Population-based, Australia	OR, 1.09 (0.75-1.59)	NHL, exposed to benzene compared with nonexposed
			OR, 1.19 (0.81-1.74)	NHL, nonsubstantial benzene exposure (some opportunity for exposure)
			OR, 0.31 (0.06-1.50)	NHL, substantial benzene exposure (probable or definite exposure for 5+ y at high frequency)
			OR, 1.45 (0.92-2.29)	NHL, substantial exposure to any solvent; trend with exposure level
Gerin et al.	1998	Population-based, Montreal	OR, 0.6 (0.4-1.0)	NHL, men with low occupational exposures to benzene (service station attendants, mechanics and machinists), compared with unexposed
			OR, 0.8 (0.4-1.6)	NHL, men with medium/high occupational exposures to benzene (paint mixers, rubber workers, chemists, and leather and shoe makers), compared with unexposed
Glass et al.	2003	Petroleum workers	OR ~ 1	NHL/MM for all cumulative lifetime benzene exposure groups; elevated leukemia risk observed
Greenland et al.	1994	Transformer manufacturing	OR, 1.0 (0.22-4.53)	Lymphoma among white males with direct benzene exposure employed before 1984, with mortality 1969-1984 reported to the pension office (i.e., vested employees)
Hardell et al.	1981	Hospital-based, Umea	RR, 4.5 (1.9-11.4)	NHL, high-grade exposures to benzene, styrene, perchloroethylene or TCE (continuously for 1+ wk, or repeatedly for brief durations 1+ mo); cases reported 1974-1978
Hardell et al.	1994	Hospital-based, Umea	OR, 28 (1.8-730)	NHL, exposed to benzene
			OR, 2.9 (1.6-5.6)	NHL, high grade exposure to organic solvents
			OR, 1.8 (0.8-3.8)	NHL, low-grade exposures to organic solvents
Kato et al.	2005	Population-based, New York	OR, 1.52 (0.41-5.70)	NHL, occupational exposure to benzene
			OR, 1.40 (1.05-2.03)	NHL, home and occupational exposure to paint thinner or turpentine

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Table 1. Case control studies of NHL with benzene exposure (Cont'd)

Author	Date	Study design	Findings	Comments
Mao et al.	2000	Population-based, Canada	OR, 1.2 (0.8-1.9)	NHL, men exposed to benzene
			OR, 0.6 (0.2-1.8)	NHL, women exposed to benzene
Miligi et al.	2006	Population-based, Italy	OR, 1.6 (1.0-2.4)	NHL, medium/high occupational benzene exposure compared with no exposure
			OR, 1.2 (0.7-2.0)	NHL, medium/high occupational benzene exposure for ≤15 y
			OR, 2.9 (0.9-9.0)	NHL, medium/high occupational benzene exposure for >15 y
			OR, 2.4 (1.3-4.5)	Diffuse NHL, medium/high occupational benzene exposure
Ott et al.	1989	Chemical workers	OR, 1.0	NHL, men ever/never exposed to benzene and ever employed 1940-1978, followed to 1978
			OR, 1.6	NHL, benzene exposure 5+ y
			OR, 3.2	NHL, foremen and maintenance/construction workers ever/never exposed to benzene
			OR, 5.2	NHL, instrument men in the maintenance/construction group ever/never exposed to benzene
Persson and Fredrickson	1999	Hospital-based, Sweden	OR, 0.8 (0.1-3.8)	NHL (B-cell origin), benzene exposure; two studies pooled: (*a*) diagnosed 1964-1986, alive 1986; (*b*) diagnosed 1975-1984, alive early 1990s
			OR, 2.6 (1.3-4.7)	NHL, exposed to white spirits
Scherr et al.	1992	Population-based, Boston	RR, 1.2 (0.5-2.6)	NHL, benzene exposure
			RR, 1.0 (0.6-1.7)	NHL, gasoline/kerosene exposure
Schnatter et al.	1996	Petroleum workers	OR, 5.85 (0.3-354)	NHL, benzene exposure 0.5-0.99 ppm at some point during career 1964-1983
			OR, 0.54 (0.01-5.94)	NHL, benzene exposure >1 ppm, one case
			OR, 1.44 (0.17-20)	NHL, benzene exposure 0.5-7.99 pm-y, 5-y lag
Wilcosky et al.	1984	Rubber workers	OR, 3.0	Lymphoreticulosarcoma, benzene exposed men ages 40-84 y, followed 1964-1974
			OR, 1.2	Lymphoreticulosarcoma, gasoline exposed men
			OR, 2.8	Lymphatic leukemia, benzene exposed men
			OR, 5.3	Lymphatic leukemia, benzene exposed men
Xu et al.	2003	Hospital-based, Sichuan	OR, 2.78	Malignant lymphoma and exposure to benzene

NOTE: Data in parentheses are 95% CIs.

Review of Case-Control Studies with Probable Benzene Exposure

We identified 43 case-control studies of NHL outcomes that recognized persons with probable occupational exposure to benzene. Forty of these 43 (93%) studies show some elevation of NHL risk, with 23 of 43 (53%) studies finding statistically significant associations between NHL risk and probable benzene exposure (Supplementary Table S1). Slightly more than half of these studies, 22 in total, specifically looked at benzene exposure and are described in Table 1. Of these 22 studies, 17 (77%) show some elevation of NHL risk, with 8 of 22 (36%) finding statistically significant associations between NHL risk and benzene exposure. The eight studies showing increased risks are diverse in nature and include the recent study of Miligi, Vineis, Costantini, and colleagues, who described an increased risk of NHL with exposure to aromatic hydrocarbon solvents of 2.1 (1.1-4.3; ref. 5). Medium/high exposure to benzene-containing solvents elevated the risk of NHL [odds ratio (OR), 1.6; 95% confidence interval (95% CI), 1.0-2.4], especially diffuse NHL (OR, 2.4; 95% CI, 1.3-4.5; Table 1; ref. 5). They update and extend their findings elsewhere in this issue.

Dryver et al. (6) found increased risks of NHL for exposures to aromatic hydrocarbon solvents and gasoline (OR, 1.72; 95% CI, 1.10-2.71; ref. 6), including dose-dependent effects for exposure to aromatic hydrocarbon solvents and duration-dependent effects for gasoline. Risks were also significantly increased for employment as an automobile mechanic, gas station attendant, and painter or varnisher. Blair et al. (7) observed that increased risks of diffuse and follicular NHL were associated with increased benzene exposure intensity and were significantly increased among both painters and persons with metal exposures.

Fabbro-Perray et al. (8) identified an association between self-reported benzene exposure and increased risk of NHL (OR 2.0; 95% CI, 1.1-3.9) that was especially strong for those exposed for >810 days (Table 1). Hardell et al. (9) reported increased risks of lymphoma in workers with high exposures to benzene, styrene, and chlorinated solvents (RR, 4.5; 95% CI, 1.9-11.4). Following up this study, Hardell et al. (10) observed large increases in NHL risk (OR, 28; 95% CI, 1.8-730) subsequent to benzene exposure; smaller, but significant, risks of NHL were observed for exposure to degreasers and organic solvents (Table 1).

Ott et al. (11) found elevated risks of NHL in foremen and others who had long careers in maintenance and construction work at chemical facilities. In particular, male workers with >5 years of occupational exposure to benzene had a 1.6-fold elevated risk of NHL. Xu et al. (12) found statistically significant excesses of lymphoma for exposure to benzene (adjusted OR, 2.78; $P = 0.001$) in a hospital-based study in China.

Cohort Studies of Refinery Workers

Petroleum refinery workers are potentially at risk of lymphoma and other cancers from exposure to benzene concentrated

Table 2. Cohort studies in the petroleum refining industry with non-Hodgkin lymphoma outcomes

Author	Date	All causes	All neoplasms	Findings	Comments
Bisby et al.	1993		SMR, 80 (70-100)	SMR, 150 (70-280)	Lymphohematopoietic cancer mortality among male refinery employees, Health Watch cohort
			SIR, 100 (80-120)	SIR, 130 (70-220)	Lymphohematopoietic cancer incidence among male refinery employees
		SMR, 64 (67-71)	SMR, 80 (70-100)	SMR, 100 (40-210)	NHL mortality, Health Watch cohort
			SIR, 96 (85-108)	SIR, 130 (70-220)	NHL incidence, Health Watch cohort
Bisby and Adams	1995		SIR, 102 (90-113)	SIR, 130 (80-200)	NHL incidence, men employed 5+ y
			SMR, 80 (70-90)	SMR, 90 (40-180)	NHL mortality, men employed 5+ y
				SIR, 140 (30-400)	Lymphoid leukemia, men employed 5+ y
Christie et al.	1991		SIR, 99 (84-116)	SIR, 170 (80-310)	NHL among those employed 5+, y cancer incidence followed 1981-1989; Health Watch cohort
				SIR, 290 (80-750)	Lymphoid leukemia, men employed 5+ y
Collinwood et al.	1996		SMR, 96 (86-106)	SMR, 132 (74-217)	NHL among those employed >1 y 1946-1987, followed to 1987
				SMR, 208 (104-371)	Other lymphatic tissue cancers among white men employed >30 y
Consonni et al.	1999		SMR, 96 (80-114)	SMR, 212 (68-478)	NHL among men employed >1 d 1949-1982, followed to 1991
				SMR, 283 (57-827)	Lymphoma, men employed 15+ y, lagged 10 y
				SMR, 402 (108-1028)	Lymphoma, men 30+ y since first employed
Dagg et al.	1992	SMR, 73 (71-76)	SMR, 81 (75-87)	SMR, 106 (63-167)	Lymphoreticulosarcoma in men who worked 1+ y at the Richmond or El Segundo refineries and 1+ d 1950-1986, followed 1986
			SMR, 69 (50-94)	SMR, 166 (34-485)	Lymphoreticulosarcoma in men 10-19 y after hire at Richmond
			SMR, 77 (50-113)	SMR, 198 (24-714)	Lymphoreticulosarcoma in men 10-19 y after hire at El Segundo
					Trend with employment duration for all lymphohematopoietic cancers
					No significant elevation of leukemia mortality
Divine and Barron	1986	SMR, 77 (73-80)	SMR, 75 (68-82)	SMR, 106 (56-188)	Lymphosarcoma among white men employed as operators >1 y, and employed at the Texaco refinery for 5+ y, and 1+ d 1947-1977; no elevation among maintenance or laboratory workers
				SMR, 132 (75-214)	Other lymphatic tissue cancers among white men employed as operators >1 y; similar elevation among maintenance workers
Huebner et al.	2000		SIR, 97 (90-105)	SIR, 106 (67-161)	NHL, white and black men employed 1+ mo 1979-1982 and 1+ d 1979-1992 at a Baton Rouge refinery and chemical plant, compared with S. Louisiana
			SIR, 103 (93-111)	SIR, 127 (68-218)	NHL, men employed 20-39 y; no NHL among those employed <20 y
				SIR, 195 (78-402)	Other named variants of NHL
				SIR, 160 (51-373)	Nodular or follicular lymphoma
				SIR, 122 (40-285)	Chronic lymphocytic leukemia
Huebner et al.	2004	SMR, 76 (73-80)	SMR, 84 (77-91)	SMR, 147 (98-211)	NHL, male employees at Baton Rouge
		SMR, 74 (70-78)	SMR, 80 (73-33)	SMR, 84 (47-139)	NHL, male employees at Baytown
				SMR, 242 (116-445)	Chronic lymphocytic leukemia among men employed at Baton Rouge refinery and petrochemical plant 1+ mo 1970-1982, followed to 1997
				SMR, 123 (40-287)	Chronic lymphocytic leukemia among men employed at Baytown
Jarvholm et al.	1997		SIR, 90 (60-130)	SIR, 120 (20-370)	Lymphoma in male refinery operators exposed to petroleum only after 1958; significant excess of leukemia
Kaplan	1986	SMR, 78 (76-81)	SMR, 87 (81-93)	SMR, 90 (51-146)	Lymphoreticulosarcoma in male employees at a number of U.S. refineries, followed to 1980
				SMR, 131 (89-188)	Other lymphatic tissue cancers in men
					No excess leukemia mortality
Lewis et al.	2000	SMR, 77 (74-79)	SMR, 87 (82-93)	SMR, 114 (61-196)	Lymphoreticulosarcoma in men employed 1+ mo at Baton Rouge, Baytown or Bayway refineries and petrochemical plants 1970-1982; followed 1992
				SMR, 110 (80-147)	Other lymphatic tissue cancers in men

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Table 2. Cohort studies in the petroleum refining industry with non-Hodgkin lymphoma outcomes (Cont'd)

Author	Date	All causes	All neoplasms	Findings	Comments
Marsh et al.	1991		SMR, 102	SMR, 816	Lymphoreticulosarcoma among men employed 30+ y at Deer Park refinery and chemical plant, and 3+ mo 1948-1972, followed to 1983; compared with county of residence
		SMR, 78	SMR, 80	SMR, 189	Lymphoreticulosarcoma among men employed in the refinery, compared with county of residence
					Trend in Lymphoreticulosarcoma and leukemia with employment duration; No elevated leukemia
McCraw et al.	1985	SMR, 76 (71-83)	SMR, 91 (77-106)	SMR, 0 (<130)	Lymphoreticulosarcoma in men employed at an Illinois refinery 1+ d 1973-1982, followed to 1983
				SMR, 126 (46-274)	Other lymphatic tissue cancers in men employed 1+ d 1973-1982, followed 1983
Rabbe et al.	1998	SMR, 82 (79-86)	SMR, 92 (84-100)	SMR, 105 (48-199)	Lymphoreticulosarcoma among men and women employed at Mobil's Beaumont refinery 1+ y 1945-1987, followed to 1987
				SMR, 140 (88-211)	NHL, men
				SMR, 158 (101-235)	Other lymphatic tissue cancers, men and women
				SMR, 233 (138-368)	Other lymphatic tissue cancers among maintenance craft workers; trend inverse to employment duration
					Leukemia mortality elevated in maintenance craft workers
Rushton and Alderson	1981	O/E, 0.84	O/E, 0.89	O/E, 1.16	Lymphosarcoma mortality, men employed continuously 1+ y 1950-1975 at any of eight British refineries
				O/E, 0.74	Reticulosarcoma mortality
Rushton and Alderson	1983	O/E, 0.85	O/E, 0.87	O/E, 0.87	Lymphosarcoma mortality, men employed in oil distribution system for 1+ y 1950-1975, followed to 1975
				O/E, 1.65	Other lymphatic tissue cancers
Schnatter et al.	1992	SMR, 91 (86-95)	SMR, 90 (81-99)	SMR, 127 (69-213)	NHL, active or living retirees as of 1964, employed 1+ y 1964-1983 as refinery workers with a Canadian petroleum company
				SMR, 244 (89-531)	Reticulosarcoma mortality among refinery workers
				SMR, 222 (56-1238)	NHL, male workers in all company segments employed <4 y, 10-y latency; 1 case
Shallenberger et al.	1992	SMR, 89	SMR, 94	SMR, 129	Lymphoreticulosarcoma among those employed 1+ mo 1970-1982 at Baton Rouge, Baytown and Bayway refineries and chemical plants, followed to 1982
				SMR, 116	Other lymphatic tissue cancers
Thomas et al.	1982	PMR, 100	PMR, 119	PMR, 132	NHL, male deceased and retired union members 1943-1979 employed at three fineries in the Beaumont/Port Aurthur area of Texas; elevated leukemia mortality
				PMR, 157	NHL, retired while male union members 1943-1979
				PMR, 137	NHL, white male union members actively employed at time of death 1943-1979
					Leukemia mortality significantly elevated
Tsai et al.	1983	SMR, 58 (40-81)	SMR, 87 (42-160)	SMR, 0	All lymphopoietic cancers among men ever employed 1952-1978 on benzene units at a Texas refinery; 0 cases observed, 1.12 expected
Tsai et al.	1992	SMR, 116 (91-146)	SMR, 109 (106-113)	SMR, 124 (33-340)	Morbidity, all lymphopoietic cancers among male production workers ever employed 1981-1988 at Deer Park refinery and chemical plant, followed to 1988
		SMR, 97 (90-104)	SMR, 92 (61-134)	SMR, 91 (10-397)	Morbidity, all lymphopoietic cancers among male staff ever employed 1981-1988
Tsai et al.	1993	SMR, 89 (84-95)	SMR, 80 (69-91)	SMR, 65 (8-236)	Lymphoreticulosarcoma among men employed 6+ mo 1973-1989 at Martinez and Wilmington refineries, and pensioners alive as of 1973, followed to 1989
				SMR, 122 (65-209)	Other lymphatic tissue cancers

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Table 2. Cohort studies in the petroleum refining industry with non-Hodgkin lymphoma outcomes (Cont'd)

Author	Date	All causes	All neoplasms	Findings	Comments
Wong et al.	1986	SMR, 72	SMR, 76	SMR, 127	Lymphoreticulosarcoma among men who worked 1+ d 1950-1980 and 1+ y before 1980 at Richmond and El Segundo refineries, followed to 1980; trend employment duration
				SMR, 163	Lymphoreticulosarcoma among men employed 15+ y
				SMR, 181	Lymphoreticulosarcoma after 10-19 y latency
				SMR, 142	Cancers other lymphatic tissues
Wong et al.	1993	SMR, 46	SMR, 68	SMR, 147	Other lymphatic tissue cancers among land-based gasoline distribution employees potentially exposed to gasoline vapors for 10-19 y, among those potentially exposed 1+ year, 1946-1985
				SMR, 118	Other lymphatic tissue cancers among land-based employees, potentially exposed 20-29 y
		SMR, 51 (49-54)	SMR, 66 (61-73)	SMR, 75 (58-97)	All lymphopoietic cancers among all land-based cohort members
		SMR, 77 (73-80)	SMR, 93 (87-101)	SMR, 73 (39-125)	Other lymphatic tissue cancers among marine-based cohort members
				SMR, 335	Other lymphatic tissue cancers among marine-based employees, potentially exposed 20-29 y
Wongsrichanalai et al.	1989	SMR, 77 (74-80)	SMR, 86 (80-93)	SMR, 99 (54-166)	Lymphosarcoma among white men ever employed 1940-1984 at an Illinois refinery,
		SMR, 79 (76-82)	SMR, 87 (80-95)	SMR, 106 (56-182)	Lymphosarcoma among male hourly workers

NOTE: Data in parentheses are 95% CIs.
Abbreviations: SMR, standardized mortality ratio; SIR, standardized incidence ratio; O/E, observed deaths by expected deaths; PMR, proportionate mortality ratio.

during the refining process. There have been many studies of workers in this industry, most of which have been conducted by industry-funded research groups. We identified 26 studies of petroleum refinery workers reporting morbidity or mortality for lymphomas and all (combined) neoplasms (Table 2). Lymphoma mortality or morbidity is significantly elevated in a few studies, but in most studies the rates are slightly but not significantly elevated. These slightly elevated rates, however, are striking because the studies report the population to have a deficit of mortality or morbidity from all (combined) neoplasms or all causes. Deficits in mortality and morbidity in cohorts of workers are often identified as the ''healthy-worker effect.'' The healthy-worker effect, however, would predict that the workers experience deficits in mortality and morbidity from *all* causes: morbidity and mortality rates near those experienced by the general population or white-collar workers are suggestive of adverse health effects from occupational exposures. Among the 26 studies reporting mortality or morbidity from all neoplasms and from NHL, 23 (88%) showed that the rate of lymphoma morbidity or mortality was higher than that for all neoplasms. A similar trend appears for studies reporting all-cause mortality: the rate of lymphoma mortality is greater than the rate of all-cause mortality in 14 of 17 (82%) of studies reporting both outcomes.

We explored this remarkably consistent finding further by adjusting for the healthy-worker effect in the study of Dagg et al. (13). Miettinen and Wang (14) proposed analyzing proportionate mortality studies as case-control studies to yield an odds ratio estimate. The same approach can be used to adjust for the healthy-worker effect. The standardized mortality ratio for lymphatic and hematopoietic cancers was not significantly elevated at 107 (95% CI, 86-132) without adjustment in this study, but the standardized mortality ratio for all causes of death was 73 (95% CI, 71-76), showing clear evidence of a healthy-worker effect. To adjust for the health worker effect, we considered lymphatic and hematopoietic cancers to be cases, and all other causes of death excluding lymphatic and hematopoietic cancers as controls. The OR for lymphatic and hematopoietic cancers estimated using Miettinen's method (14) was 1.48 (95% CI, 1.20-1.83; $P < 0.001$), providing clear evidence that the healthy worker effect masked increased blood cancer risks. Many cohort studies of refinery workers in Table 2, like the study by Dagg et al. (13), show reduced standardized mortality ratios for all neoplasms combined, suggesting that masking of NHL risk by the healthy-worker effect is common. A comprehensive reevaluation of these studies with appropriate adjustments should be undertaken.

Studies of Other Worker Cohorts

A study of benzene-exposed workers in China, conducted by investigators from the U.S. National Cancer Institute and the Chinese Academy of Preventive Medicine, is ongoing (15). To date, the primary NHL-related finding from the ~74,000 observed workers is a 3-fold increase in NHL risk for benzene-exposed workers, increasing to a 4-fold excess in NHL risk for workers exposed to benzene for 10 or more years. For workers in the chemical industry in this cohort, the relative risk (RR) was even higher at 7.8. In a study of chemical industry workers in the United States, Wong (16) found that the RR for NHL mortality among white benzene-exposed workers was 8.6 ($P = 0.02$) compared with unexposed workers. For workers continuously exposed to benzene, the RR was 9.6 compared with unexposed workers. Cohort studies of workers in the chemical manufacturing industry are summarized in Supplementary Table S2.

Studies of worker cohorts in the rubber industry, like the petroleum refining and chemical industries, have found elevated risks of lymphatic and hematopoietic malignancies (Supplementary Table S3). The role of benzene in these cancers, however, can be difficult to define because workers in this

industry are often exposed to other potential carcinogens, such as 1,3-butadiene. The only study of rubber workers in which it is widely agreed that the only significant solvent exposure was benzene is the Pliofilm study of rubber hydrochloride workers (17, 18). Although significantly elevated risks for leukemia and multiple myeloma were observed, an elevated risk for NHL was not. The failure of this study to identify an association between benzene exposure and NHL mortality, however, does not exclude the possibility of the association. In particular, the low mortality and long latency of NHL severely limited the power of the Pliofilm study to detect an association between benzene-exposure and NHL mortality. We note that the 5-year survival of NHL and lymphocytic leukemias exceeds 60%, compared with <20% for acute leukemia and myeloma. This explains why the expected number of deaths from NHL in the Pliofilm cohort was less than those expected from acute leukemia, although the incidence of NHL is four to five times that of leukemia. Further, the typical latency period for NHL is likely to be much longer than that for acute leukemia. Thus, the Pliofilm study has limited power to detect elevated risks of NHL following benzene exposure.

Elevated Risks of Chronic Lymphocytic Leukemia

B-cell chronic lymphocytic leukemia is now classified together with small lymphocytic lymphoma as a form of NHL. A number of studies show elevated risks of chronic lymphocytic leukemia at relatively low levels of benzene exposure (Supplementary Table S1). The most notable is that of Glass et al. (19), but others have also showed elevated risks including studies in the United Kingdom of petroleum distribution workers (20).

Other Evidence Supporting an Association between Benzene Exposure and Lymphoma

Numerous studies have reported associations between benzene exposure and the induction of lymphomas in mice. Studies by Cronkite et al. (21) and Snyder et al. (22) in the early 1980s showed inhalation of benzene caused excess lymphomas in various mouse strains. The 1986 National Toxicology Program carcinogenicity bioassay of benzene also reported an excess of malignant lymphomas, as well as other cancers, in male and female B6C3F1 mice. Studies in Italy by Maltoni et al. (23) showed excesses of lymphosarcomas in RF/J mice. As with many rodent toxicology studies, there has been debate over the relevance of these findings to humans.

There are many similarities between leukemia induced by benzene and that induced by chemotherapy with alkylating agents, so-called therapy-related leukemia, and the latter has been proposed as a model of chemical-induced leukemogenesis (24). Treatment of primary cancers with alkylating agents such as melphalan dramatically increases risks of secondary leukemias. Interestingly, as discussed by Krishnan and Morgan in this issue, numerous studies show that alkylating agent chemotherapy also increases the risk of secondary NHL as well as leukemia. Thus, benzene may act like alkylating agents and ionizing radiation in inducing both leukemias and lymphomas.

Conclusions

A comprehensive review of all case-control and cohort studies that identified probable occupational exposures to benzene and NHL morbidity or mortality showed evidence of an association between occupational benzene exposure and NHL. Studies in experimental animals and of therapy-related lymphoma in the clinical setting support this finding. Potential mechanisms for lymphoma induction by benzene include immunotoxicity and chromosomal damage resulting in translocations and deletions. Further work is needed to elucidate these mechanisms.

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